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Research article

Correlation between computed tomography features and clinical characteristics in HIV-negative patients with pulmonary cryptococcosis

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Abstract

Objective: To analyze the correlations between CT features and clinical characteristics in HIV-negative patients with pulmonary cryptococcosis.
Methods: Medical records of 16 HIV-negative patients with pulmonary cryptococcosis diagnosed at our institution were retrospectively analyzed. CT examinations were obtained with a multidetector row CT scanner. The clinical characteristics of 7 patients with nodules or masses without ground-glass opacity (GGO)/consolidation type were compared with those of 9 patients with inclusive GGO or consolidation type.
Results: Host status was immunocompromised (81.2%) in most of the patients. 6 (37.5%) patients were asymptomatic. The most frequent CT findings were one or more nodules (87.5%), GGO (42.9%), and consolidations (18.8%). Most lesions were located in the lower lobes. The levels of hemoglobin (12.0 [8.9–16.5] vs 8.4 [4.4–14.9]) and platelets (24.6 [10.2–36.0] vs 8.4 [1.4–30.3]) were significantly lower in patients with inclusive GGO or consolidation type compared with those of patients without GGO or consolidation ($p = 0.044$ and $p = 0.023$, respectively). There was no statistically significant difference in sex, age, host status, body mass index, symptoms at initial consultation, HbA1c, WBC, lymphocytes, albumin, ESR, CRP, and IgG.
Conclusions: GGO or consolidation was more common in HIV-negative patients with cryptococcosis when they suffered from anemia and thrombocytopenia.

Keywords: Lung; Tomography; X-ray computed; Infection

1. Introduction

Cryptococcosis, which occurs sporadically worldwide, is a potentially serious fungal disease that is typically caused by inhalation of *Cryptococcus neoformans* or *C.gattii*, which tends to form an aerosol [1]. The fungus most commonly infects patients with human immunodeficiency virus (HIV) and other causes of reduced immunity, and it less frequently infects immunocompetent patients. The respiratory tract is thought to be the entry site and is the organ most frequently involved when cryptococcal infection develops [2,3]. The presentation of pulmonary cryptococcosis can range from asymptomatic nodular disease to severe acute respiratory distress syndrome (ARDS). In an immunocompetent host the pulmonary infections normally are asymptomatic, different from the immunocompromised patient, in which cryptococcal infections often cause symptomatic infection, often disseminate to the central nervous system, skin, and bones.

The CT findings of pulmonary cryptococcosis are varied. Well-defined single or multiple pulmonary nodules are the

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most frequent radiologic abnormality, followed by pulmonary infiltrates. Furthermore, cavitation within nodules and parenchymal consolidation are more common in immunocompromised than in immunocompetent patients [3]. K. Kishi et al. reported that ground-glass opacity (GGO) or consolidation may be a radiological finding of pulmonary cryptococcosis [4]. They also reported that there might be a correlation between CT features and clinical characteristics in patients with GGO and patients without GGO. But the correlation is not clear. So far few investigations have compared the lesions with/without GGO and clinical characteristics of pulmonary cryptococcosis in non-HIV patients [5−8]. As a result, we retrospectively reviewed pulmonary cryptococcosis patients and assessed the correlation between chest CT features and clinical characteristics.

2. Material and methods

This was a retrospective study in which clinical data were collected from patient medical records. Baseline clinical measurements were obtained within 7 days of the diagnosis of pulmonary cryptococcosis. We studied 16 HIV-negative patients with pulmonary cryptococcosis diagnosed by histological or cytological presence of the organism in lung biopsy specimens, by positive findings from culture of respiratory specimens, or by a positive result of the serum cryptococcal antigen test with radiographic evidence of pulmonary disease. The patients were diagnosed at our institution from January 2010 to January 2015.

Ten patients were men and 6 were women, with a median age of 60 [range: 25−82] years. Host status was immunocompromised in 81.2% of the patients, of whom 5 patients had hematologic malignancy, 3 patients received corticosteroid and/or other immunosuppressive drugs for myasthenia gravis, 2 patients with advanced solid tumor, 2 patients received corticosteroid for chronic nephritis, and 1 patient received renal transplantation. 87.5% of patients did not have impaired glucose tolerance (hemoglobin A1c (HbA1c) < 6.5%), and 6 (37.5%) were asymptomatic. Fever and cough were the most common presenting symptoms, followed by general fatigue. Elevation of the peripheral white blood cell (WBC) count was detected in 6 patients (36.5%) (normal range: 3200−9000/μL). A lymphocyte cell count of <1000/μL was present in 7 (43.8%) patients, a hemoglobin (Hb) of <10 g/dL in 7 (43.8%) patients, a platelet count (Plt) of <15.0 × 104/μL in 7 (43.8%) patients, an albumin level of <3.0 g/dL in 6 (36.5%) patients, and a low immunoglobulin G (IgG) of <800 mg/dL) in 6 (36.5%) patients. All patients were positive for cryptococcal antigen titer.

The diagnosis of pulmonary cryptococcosis was made by direct tissue examination in 5 patients (transbronchial lung biopsy in 4 and video-assisted thoracoscopic surgery in 1), and by cytology from bronchial brushings and washing in 2 patients. The other 9 patients were diagnosed clinically by the positive result of a serum cryptococcal antigen test with radiographic evidence of pulmonary disease. Treatment included antifungal drugs alone in 10 patients, surgery plus antifungal therapy in 1, and none in 4 patients. Of the 11 patients who received antifungal therapy, 10 patients improved, and 1 died due to underlying disease during the follow-up period. Underlying disease in the 4 patients who received no treatment (hematological malignancy in 3 and pancreatic cancer in 1) progressed rapidly, and antifungal treatment was impossible.

CT examinations were obtained with a multidetector row CT scanner (Lightspeed Qx/i; GE Medical Systems, Milwaukee, WI). Imaging parameters were as follows: 120 kVp, 180 mAs, 1.25-mm collimation and a pitch of 1.5. The reconstructed slice thickness and interval were 3 mm. The routine chest CT images were obtained from the lung apices through the bases. Images were viewed on standard lung windows (level −600 HU; width 1500 HU) and mediastinal windows (level 40 HU; width 400 HU).

The chest CT images were analyzed by consensus by two radiologists (JQ and YW, with 15 and 10 years of experience in chest imaging, respectively). They were blinded to the diagnosis or clinical data. A consensus reading of the CT images was conducted by two observers. The findings and interpretations were based on their consensus opinion. CT images were assessed for the following patterns of pulmonary abnormality: nodules, GGO, and consolidations. Consolidation was considered to be present when the opacities obscured the underlying vessels. Nodules were defined as <3 cm in diameter and a mass was defined as ≥3 cm in diameter. Ground-glass opacity was defined as hazy increased attenuation of the lung without obscuration of the bronchial and vascular margins.

In order to analyze the correlations between CT features and clinical characteristics in HIV-negative patients with pulmonary cryptococcosis, we divided the patients into two groups: 7 patients with nodules or masses without GGO/consolidation type; 9 patients with inclusive GGO or consolidation type.

Data are presented as median [range] unless otherwise stated. Fisher's exact test or Mann−Whitney *U* test was used for between-group comparisons with nominal and continuous variables, respectively. A p value < 0.05 was considered statistically significant. Missing data were categorized as "unknown" and were entered into each statistical analysis model. All data were analyzed with SPSS version 20.0 for windows.

3. Results

3.1. Clinical characteristics

The clinical characteristics of the 7 patients with a nodule or mass without GGO/consolidation type were compared with those of the 9 patients with inclusive GGO or consolidation type and are were summarized in Table 1. Neither sex, age, host status, body mass index (BMI), symptoms at initial consultation nor HbA1c, WBC, lymphocytes, albumin, ESR, CRP, IgG were significantly different between the two groups.

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3.2. CT features

The pulmonary abnormalities seen on the initial CT scans are summarized in Table 2. No patient had extra thoracic cryptococcosus. The most common CT findings were one or more pulmonary nodules (87.5%). A solitary nodule was seen in 18.8% (Fig. 1A) and multiple nodules in 68.7% (Fig. 1B) of patients. The second most common finding was GGO (42.9%) (Fig. 2A). Other associated findings included consolidations (18.8%) (Fig. 2B), pleural effusion (25.0%), and calcification (6.3%). Lesions in the right lung were present in 13 (81.3%) patients, in the left lung in 8 (50.0%) patients, and in bilaterally in 5 (31.3%) patients, of whom the lesions were more frequent in the right lung. 10 (62.5%) patients had lesion involvement in the lower lobe, 6 (42.9%) patients had upper lobe involvement, and 3 (18.8%) patients had middle lobe involvement, which was more frequent in the lower lobe. Lesion extent was evaluated in the pulmonary lobes, including the upper, middle, and lower lobes in the right lung, and the upper lingular and lower lobes in the left lung. Most lesions (62.5%) were located in one lobe, and no lesions were located in 4 or more lobes.

Table 2
CT features of pulmonary abnormalities.

Abnormality	n (%)
Pulmonary nodules	14 (87.5)
Solitary	3 (18.8)
Multiple	11 (68.7)
5-10	5 (31.3)
> 10	0 (0)
Ground-glass opacity	6 (42.9)
Consolidations	3 (18.8)
Pleural effusion	4 (25.0)
Calcification	1 (6.3)
Lesion area	
Right lung	13 (81.3)
Left lung	8 (50.0)
Bilateral lungs	5 (31.3)
Lesion area	
Upper lung	6 (42.9)
Middle lung	3 (18.8)
Lower lung	10 (62.5)
Extent of lesions (5 pulmonary lobes)	
1/2/3	10 (62.5)/5 (31.3)/1 (6.3)
>4	0 (0)

3.3. Correlation between CT features and clinical characteristics

The hemoglobin (12.0 [8.9–16.5] vs 8.4 [4.4–14.9]) and platelets (24.6 [10.2–36.0] vs 8.4 [1.4–30.3]) were significantly lower in patients with inclusive GGO or consolidation type compared with those of patients without GGO or consolidation ($p = 0.044$ and $p = 0.023$, respectively). GGO or consolidation was more common in HIV-negative patients with cryptococcosis when they suffered from anemia and thrombocytopenia.

4. Discussion

Cryptococcosis typically occurs in immunocompromised patients such as those with HIV/AIDS, and the presence of

Table 1
Clinical characteristics of patients with a nodule or mass without GGO/consolidation type and with inclusive GGO or consolidation type.

Clinical characteristics	Nodule or mass without GGO/consolidation type	Inclusive GGO or consolidation type	P Value
Male	5 (71.4%)	5 (55.5%)	0.633
Age (years)	73 [25–82]	60 [56–79]	0.873
>70 years	4 (57.1%)	4 (44.4%)	0.999
Immunocompromised	5 (71.4%)	8 (88.9%)	0.550
BMI, kg/m^2	19.6 [16.0–24.0]	22.1 [17.6–25.0]	0.153
<18.5 kg/m^2	2 (28.6%)	1 (11.1%)	0.550
No Symptoms	3 (42.9%)	3 (33.3%)	0.999
HbA1c (%)	5.8 [5.1–6.5]	5.5 [4.9–7.0]	0.943
WBC (/μL)	7400 [6400–12,300]	8100 [1500–31,400]	0.427
Lym (/μL)	1300 [600–2900]	600 [230–2200]	0.265
<1000/μL	2 (28.6%)	5 (55.6%)	0.358
Hb (g/dL)	12.0 [8.9–16.5]	8.4 [4.4–14.9]	**0.044**
<10.0 mg/dL	1 (14.3%)	6 (66.7%)	0.060
Plt ($\times 10^4$/μL)	24.6 [10.2–36.0]	8.4 [1.4–30.3]	**0.023**
<10.0 $\times$ 10^4/μL	0 (0%)	5 (55.6%)	**0.034**
Albumin (g/dL)	3.3 [2.5–4.9]	2.9 [2.4–3.9]	0.184
<3.0 g/dL	1 (14.3%)	5 (55.6%)	0.145
ESR (mm/hr)	10 [1–62]	74 [10–78]	0.176
CRP (mg/dL)	0.5 [0.1–7.0]	1.4 [0.1–6.7]	0.310
≥1.0 mg/dL	1 (14.3%)	6 (66.7%)	0.060
IgG (mg/dL)	885 [467–2507]	983 [410–4121]	0.897
<800 mg/dL	3 (42.9%)	3 (37.5%)	0.999

Values are shown as median [range] or number (%). Statistically significant p-values are shown in bold.
Abbreviations: GGO: ground-glass opacity, BMI: body mass index, HbA1c: hemoglobin A1c, WBC: white blood cell, Lym: lymphocyte cell, Hb: hemoglobin, Plt: platelet, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, IgG: immunoglobulin G.

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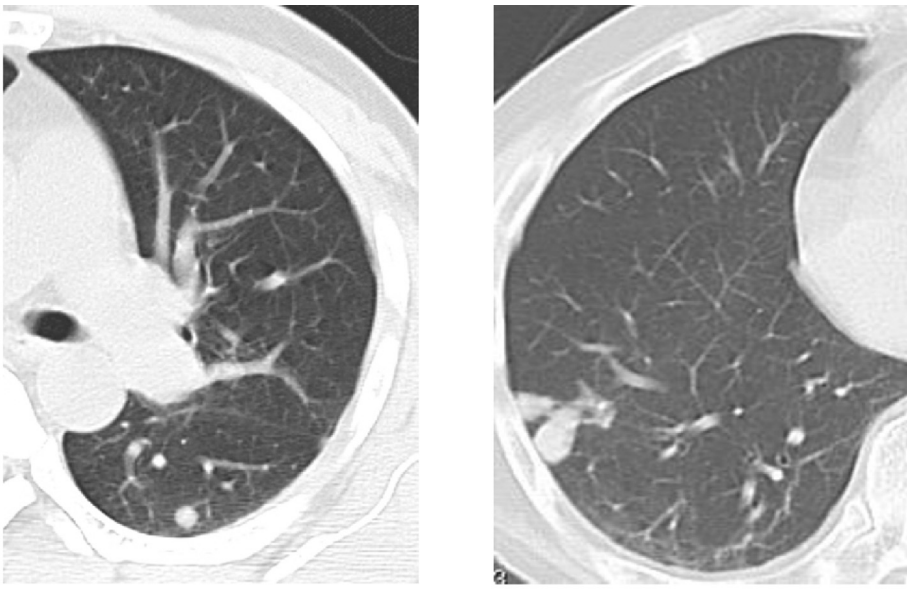
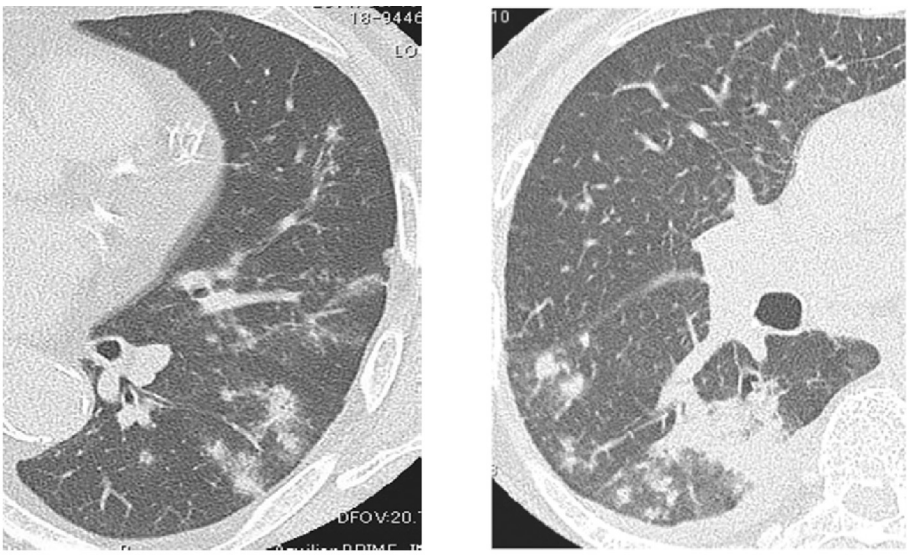


A B

Fig. 1. Pulmonary cryptococcosis of the nodule without GGO/consolidation type. One patient showed a solid nodule without spiculation in the left lower lobe (A). Another patient showed two nodules in the right lower lobe (B).



A B

Fig. 2. Pulmonary cryptococcosis in inclusive GGO or consolidation type. One patient showed multiple nodules with GGO in the left lung (A). Another patient showed multiple nodules, consolidation, and pleural effusion in the right lower lobe (B).

pulmonary *Cryptococcus* sp. in HIV/AIDS patients is associated with high mortality [9,10]. The clinical descriptions of pulmonary cryptococcosis in HIV-negative individuals are quite limited because of the rarity of the disease itself. In general, males are more frequently infected than females [11,12]. In the present study, the disease also occurred predominantly in males. Nadrous et al. reported that about one-third of immunocompetent patients with pulmonary cryptococcosis were asymptomatic [13]. Although the present study comprised predominantly immunocompromised patients (81.2%), a similar ratio of asymptomatic patients was also observed, indicating that even asymptomatic patients with immunodeficiency require attention.

The CT features of pulmonary cryptococcosis were variable. Most of our patients (87.5%) had pulmonary nodules (solitary: 18.8%, multiple: 68.7%). The high frequency of these lesions was consistent with that reported by other studies [8,11,12,14,15]. The lesions were located predominantly in the lower lung (62.5%) rather than in the middle (18.8%) or upper lung (42.9%), which was also been noted in other studies [11,12,16,17], and were found mainly in the right (81.3%) rather than the left (50.0%) lung in most patients. Most lesions

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were found in a single lobe (62.5%), and no lesions were present in 4 or more lobes.

We investigated the correlation between clinical characteristics and chest CT features in the patients with pulmonary cryptococcosis. GGO lesions and consolidations of pulmonary cryptococcosis appear to occur more frequently in immunocompromised hosts [3]. Individuals with macrophages, helper T cells, natural killer cells, and others are related to infection with *C. neoformans* [18]. We found GGO lesions in 42.9% and consolidations in 18.8% of the patients. Inclusive GGO or consolidation type was more frequent in the immunocompromised hosts (88.9%), but the frequency of lesions without GGO/consolidation type in these hosts was nearly the same (71.4%). Generally, an "immunocompromised host" refers to a patient with malignant disease or who has received an immunosuppression drug, has undergone an enforced transplantation, has severe diabetes, or is immunodeficient, but the definition of "immunocompromised host" is not yet clear. Therefore, we thought that the assessment of clinical data and radiological features related to pulmonary cryptococcosis may be useful because non-HIV patients also have pulmonary cryptococcosis. Results of routine laboratory investigations in another study were generally nonspecific [7]. The levels of Hb and Plt were significantly lower in the patients with inclusive GGO or consolidation type than in those with nodule or mass without GGO/consolidation type. Although approximately one third of our patients had hematologic malignancy, the lymphocyte cell count and IgG level as indices of immunosuppression were not significantly difference between the two disease types. Therefore, the CT findings of pulmonary cryptococcosis in patients with anemia and thrombocytopenia might indicate GGO or consolidation.

There are some reports on the distinction between immunocompetent and immunocompromised patients. Xie et al. found that cavitations within nodules/masses were more commonly seen in immunocompromised patients, especially AIDS patients, while air bronchograms were more commonly seen in immunocompetent patients [11]. The same as we found in our patients. In the present manuscript, we mainly analyzed and focused on the correlations between CT features and clinical characteristics in HIV-negative patients with pulmonary cryptococcosis. So we did not divide the patients into groups with immunocompromised and competent.

A limitation of this study is that it is a retrospective, single-site study with a small number of patients collected over a long period, and our results should not be generalized to the worldwide population. Further studies are needed to clarify the correlation between CT findings and clinical characteristics in patients with pulmonary cryptococcosis.

5. Conclusion

We conclude that GGO or consolidation was more common in HIV-negative patients with cryptococcosis when they suffered from anemia and thrombocytopenia.

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References

[1] Chang WC, Tzao C, Hsu HH, Lee SC, Huang KL, Tung HJ, et al. Pulmonary cryptococcosis: comparison of clinical and radiographic characteristics in immunocompetent and immunocompromised patients. Chest 2006;129(2):333−40.
[2] Wang JM, Zhou Q, Cai HR, Zhuang Y, Zhang YF, Xin XY, et al. Clinicopathological features of pulmonary cryptococcosis with cryptococcal titan cells: a comparative analysis of 27 cases. Int J Clin Exp Pathol 2014;7(8):4837−46.
[3] Rodríguez-Cerdeira C, Arenas R, Moreno-Coutiño G, Vásquez E, Fernández R, Chang P. Systemic fungal infections in patients with human inmunodeficiency virus. Actas Dermosifiliogr 2014;105:5−17.
[4] Kishi K, Homma S, Kurosaki A, Kohno T, Motoi N, Yoshimura K. Clinical features and high-resolution CT findings of pulmonary cryptococcosis in non-AIDS patients. Respir Med 2006;100(5):807−12.
[5] Suwatanapongched T, Sangsatra W, Boonsarngsuk V, Watcharananan SP, Incharoen P. Clinical and radiologic manifestations of pulmonary cryptococcosis in immunocompetent patients and their outcomes after treatment. Diagn Interv Radiol 2013;19(6):438−46.
[6] Ye F, Xie JX, Zeng QS, Chen GQ, Zhong SQ. Zhong NS.Retrospective analysis of 76 immunocompetent patients with primary pulmonary cryptococcosis. Lung 2012;190(3):339−46.
[7] KH1 Choi, Park SJ, Min KH, Kim SR, Lee MH, Chung CR, et al. Treatment of asymptomatic pulmonary cryptococcosis in immunocompetent hosts with oral fluconazole. Scand J Infect Dis 2011;43(5):380−5.
[8] Yu JQ, Tang KJ, Xu BL, Xie CM, Light RW. Pulmonary cryptococcosis in non-AIDS patients. Braz J Infect Dis 2012;16(6):531−9.
[9] Marques VL, Gomes RC, Viola GR, Maia MM, Durigon GS, Aikawa NE, et al. Pulmonary cryptococcosis in childhood systemic lupus erythematosus and Sjögren syndrome overlap: a rare opportunistic infection. Lupus 2013;22(13):1409−12.
[10] Li J, Wang N, Hong Q, Bai C, Hu B, Tan Y. Duodenal cryptococcus infection in an AIDS patient: retrospective clinical analysis. Eur J Gastroenterol Hepatol 2015;27(3):226−9.
[11] Xie LX, Chen YS, Liu SY, Shi YX. Pulmonary cryptococcosis: comparison of CT findings in immunocompetent and immunocompromised patients. Acta Radiol 2015;56(4):447−53.
[12] Yanagawa N, Sakai F, Takemura T, Ishikawa S, Takaki Y, Hishima T, et al. Pulmonary cryptococcosis in rheumatoid arthritis (RA) patients: comparison of imaging characteristics among RA, acquired immunodeficiency syndrome, and immunocompetent patients. Eur J Radiol 2013;82(11):2035−42.
[13] Nadrous HF, Antonios VS, Terrell CL, Ryu JH. Pulmonary cryptococcosis in nonimmunocompromised patients. Chest 2003;124(6):2143−7.
[14] Lindell RM, Hartman TE, Nadrous HF, Ryu JH. Pulmonary cryptococcosis: CT findings in immunocompetent patients. Radiology 2005;236(1):326−31.
[15] Denis B, Lortholary O. Pulmonary fungal infection in patients with AIDS. Rev Mal Respir 2013;30(8):682−95.
[16] Chopra S, Capoor MR, Mallik R, Gupta S, Ray A, Khanna G, et al. Pulmonary cryptococcosis in HIV- sero-negative patients: case series from India. Mycoses 2015;58(5):288−93.
[17] Fox DL, Müller NL. Pulmonary cryptococcosis in immunocompetent patients: CT findings in 12 patients. AJR Am J Roentgenol 2005;185(3):622−6.
[18] Wozniak KL, Young ML, Wormley Jr FL. Protective immunity against experimental pulmonary cryptococcosis in T cell-depleted mice. Clin Vaccine Immunol 2011;18(5):717−23.

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